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### ***Pythium insidiosum*: The silent killer of mammals (Leonel Mendoza--02/20/98)**

#### **Introduction and History**

The genus *Pythium* comprises about eighty-five species. *Pythium* species are common pathogens causing disease in plants and fishes. The species of this genus are among the most destructive plant pathogens, inflicting serious economic losses of crops by destroying seed, storage organs, roots, and other plant tissues. *Pythium insidiosum* is the only species reported to cause infections in mammals. The disease caused by this unique microorganism has been termed pythiosis insidiosi and can cause life threatening infections in cats, dogs, cattle, equines, captive polar bears, and humans.

The first published reports of infections caused by *P. insidiosum* were last century in equines with cutaneous granulomas in Florida (USA) and India. Its true etiology, however, was not established. Although several sporadic reports of the disease in equines were made during the beginning of the 20th century, it was not until 1961 that the name *Hypomyces destruens* was proposed by Bridges and Emmons (*JAVMA* 38:579; 1961) to describe a sterile filamentous microorganism isolated from several cases of cutaneous granulomas in Texas. Later, the binomial *Pythium insidiosum* was proposed by de Cock *et al.*, (*J. Clin. Microbiol.* 25:344;1987). These investigators found that all *P. insidiosum* isolated from humans and animals around the world belonged to the single species *P. insidiosum*. Thus, other binomials used to address this organism became its synonyms.

#### **Taxonomy and Distribution.**

Members of the genus *Pythium* have been described as "aquatic fungi". However, they are not true fungi (Kingdom Fungi), they belong to the Kingdom Chromista, Class Oomycetes, Family Pythiaceae (*Acta Protozool.* 33:1-51; 1994). In culture, *P. insidiosum* develops sparsely septate hyphae similar to those

produced by the Zygomycetes (true fungi). Like other Oomycetes, *P. insidiosum* produces motile zoospores (asexual stage) when exposed to damp conditions. The zoospores are single cells with two lateral flagella that swim to find a new plant host. Once in contact with the host the zoospores lose their flagella and encyst. It is believed that zoospores act as infecting units once in contact with a mammalian host (*J. Mycol. Med.* 6:151; 1996). Under special conditions *P. insidiosum* develops globose oogonia (sexual stage) typical of this species. Pythium species are ubiquitous in soil and aquatic environments. They are worldwide in distribution and have a broad and diverse host range. *Pythium insidiosum* is reported more frequently in tropical and subtropical regions of the world. However, cases in temperate areas of Japan and USA indicate that this organism can be found in cooler environments as well. Well documented cases have been reported in Australia, the Pacific islands, Asia, and the Americas.

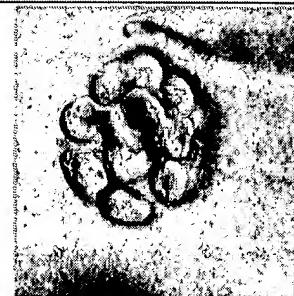


Figure 1. Wet mount of a sporangium of *Pythium insidiosum*.

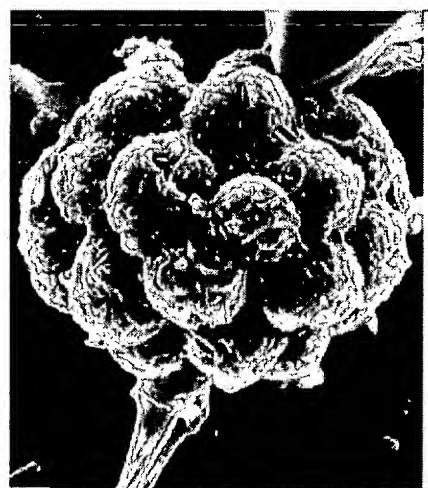


Figure 2. Scanning electron micrograph of a mature sporangium. Note well developed zoospores and flagella.

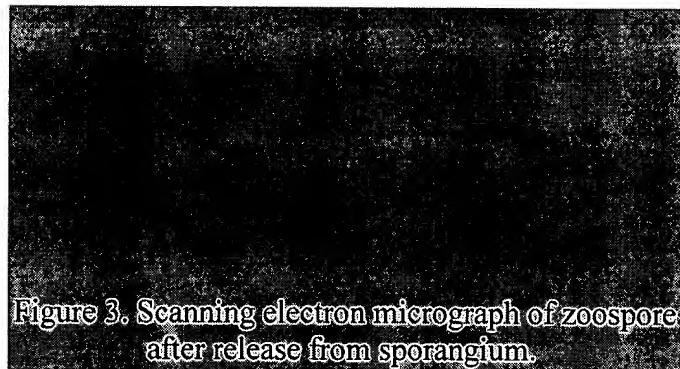
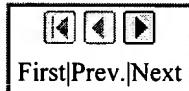


Figure 3. Scanning electron micrograph of zoospore after release from sporangium.

In Australia, the disease is restricted to eastern tropical coastal region. In Indonesia, the disease has been reported in islands of Borneo, Java, and Sumatra. In Asia, Japan, Thailand, and India are the countries with more cases of human and animal pythiosis insidiosi. Thailand alone had reported more than forty human cases caused by *P. insidiosum* since 1989. In the Americas, the disease has been reported in Brazil, Colombia, Costa Rica, Haiti, Argentina, and the USA. In the USA pythiosis insidiosi is more frequent in the States along the Gulf of Mexico specially Florida, Louisiana, and Texas where the disease is endemic. Sporadic cases have been recorded in the past ten years in dogs, equines (and even in a captive polar bear) in Georgia, Missouri, North Carolina, South Carolina, Tennessee, and Illinois.

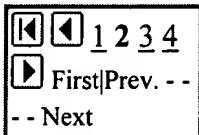
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### Epidemiology and Pathogenesis

Usually the disease is acquired after direct contact with zoospores, or other propagules of *P. insidiosum*, through a skin or mucous membrane injury. It has been well documented that *P. insidiosum* zoospores have an special tropism for open wounds as well as plant tissue (*J. Clin Microbiol.* 31:2967; 1993). This feature allows *P. insidiosum* to direct itself to a new host to complete its life cycle. Once in contact with the host, the zoospores encyst and produce a germ tube that mechanically penetrates the tissue. This happens to mammals entering swampy areas contaminated with this oomycete. In cases of intestinal pythiosis insidiosi in dogs, the infection is usually acquired after ingestion of contaminated water with zoospores. Once in the tissue the host initiates a cell mediated immunoresponse against *P. insidiosum* hyphae. This immunoresponse, however, does not prevent the propagation of the organism into healthy tissue. Most of the damage caused by *P. insidiosum* in tissues is attributed to the release of chemicals from degranulated cells, specially eosinophils and mast cells.

### Clinical and Pathological Features of Pythiosis insidiosum

The clinical and pathological changes occurring during *P. insidiosum* infections have been well documented in recent reviews (*J. Med. Mycol.* 6:151; 1996, *Curr. Top. Med. Mycol.* 7:43; 1996, *Vet. Clin. North Am. Equine Pract.* 11:91; 1995). The general clinical and pathological aspects of pythiosis insidiosi in humans and other animals are described in the following sections.

#### **Equine Pythiosis Insidiosi.**

Equine pythiosis insidiosi was first described some time in the last century, but it was not until 1961 that its true nature was determined. The disease in equines has been known under several names such as: equine espundia, Florida horse leeches, leeches, granular dermatitis, hyphomycosis destruens equi, phycomycosis, summer

sores (*llaga brava*, *llaga de verano*), and swamp cancer. Infections caused by *P. insidiosum* in equines are characterized by the formation of cutaneous granulomas. The lesions are more frequently found in body areas first in contact with swampy waters (extremities, thorax, abdomen, and head). The cutaneous granulomas caused by this organism in equines are circular in shape with a characteristic serosanguineous discharge and odor. Lesions seem to be painless, but they are extremely pruritic (itchy). In some cases the lesions are so itchy that the horse bites the affected tissue, complicating the infection. Lesions caused by *P. insidiosum* are also found in bones, intestines, and lungs but these manifestations are more rare. In addition, equine pythiosis insidiosi is clinically similar to a parasitic infection known as equine cutaneous habronemiasis.

In histopathological preparations, *P. insidiosum* produces abundant microabcesses with eosinophils, macrophages and other inflammatory cells. In chronic cases small masses called "kunkers" are observed within the infected granulomas. The coenocytic hyphae (aseptate hyphae) of this oomycete are always found within these masses.

The diagnosis of pythiosis insidiosi in horses is made by culture, histopathology, and/or serology. *Pythium insidiosum* readily grows in Sabouraud agar (+ chloramphenicol) producing aseptate sterile hyphae. In wet preparations containing different ions (specially Ca cations) *P. insidiosum* produces sporangia with zoospores. Histopathologically *P. insidiosum* can be mistaken with hyphae of the Zygomycetes (fungi). However, an immunoperoxidase assay is available to specifically detect the organism in the infected tissues. Two serological tests have been used in the past ten years: they are; immunodiffusion (ID) and Pythium-ELISA. Both are specific but the ELISA is more sensitive (*J. Clin. Microbiol.* 23:813; 1986, *Clin. Diag. Lab. Immunol.* 4:715; 1997). In addition, western blot analysis shows to be of value in the investigation *P. insidiosum* immunogens during infection (*J. Clin. Microbiol.* 30:2980; 1992).

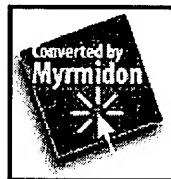
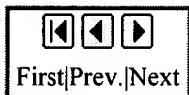
The traditional treatment of equine pythiosis insidiosi is radical surgery of the cutaneous granulomas. Recently, a neodymium-yttrium-aluminum-garnet (YAG) laser for treatment of pythiosis granulomas in two horses was successfully applied (*JAVMA* 211:464; 1997). Amphotericin B and iodides have been used in the

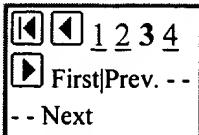
chemotherapy of equine pythiosis. However, both drugs are toxic and the results obtained over the past twenty years are controversial. Immunotherapy using a vaccine proved to be very successful to cure the disease in equines. This curative vaccine contains proteins of *P. insidiosum* and it is recommended in horses with active pythiosis insidiosi (*Mycopathologia* 119:89; 1992, *The Compendium* 15:491; 1993). The vaccine has been successful in more than 300 cases. Presently, its prophylactic (protective) features are under investigation. If the infection is not treated in the initial stages it is 100% fatal.

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### Dog Pythiosis Insidiosi

Infections caused by *P. insidiosum* in dogs have been reported in endemic areas of the United States and in other countries. The disease is characterized by developments of cutaneous and intestinal granulomas. As in equines, the disease in dogs is acquired through skin or mucous membrane injury. Dogs residing in the country side and those visiting endemic areas are prone to infection.

Two clinical signs are often observed in dogs infected with this oomycete: cutaneous lesions, and gastrointestinal granulomatous lesions. Cutaneous pythiosis in dogs is acquired through traumatic implantation of *P. insidiosum* into the skin, whereas gastrointestinal pythiosis insidiosi is acquired through ingestion of water contaminated with zoospores. The skin lesions are usually present on the legs, face and tail. Cutaneous lesions are itchy with sinus tracts. Ulceration of the original skin granulomas are frequent. Intestinal pythiosis insidiosi in dogs is characterized by severe weight loss, vomiting and diarrhea. The granulomatous gastrointestinal masses caused by *P. insidiosum* mimic those observed in neoplastic diseases, thus differential diagnosis is crucial. If not treated the disease is lethal.

As in equine pythiosis insidiosi the diagnosis is based on cultural, histopathological, and serological techniques. The most important methods for diagnosis are the immunoperoxidase and the immunodiffusion tests. Culture is also important, but just a few laboratories have the expertise required to identify this pathogen.

If the infection is not detected early the infected dogs usually die. According to recent data the number of dogs having this disease has enormously increased in the past five years. This is due to increasing awareness of *P. insidiosum* in endemic areas and the dissemination of knowledge about its clinical, diagnostic, and epidemiological features. Treatment in most cases is not successful due to the chronicity of the lesions.

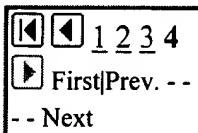
### Pythiosis Insidiosi in Other Animals

In addition, pythiosis insidiosi has been reported in several cats, cattle, and in a captive polar bear. In these cases the infection was localized in the subcutaneous tissues. The diagnosis and treatment is similar to those used in dogs and equines.

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### **Pythiosis Insidiosi in Humans**

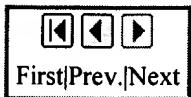
Human pythiosis insidiosi is characterized by the formation of subcutaneous lesions and the invasion of the main arteries. If not treated the infection is fatal. The majority of the cases have been diagnosed in Thailand. The disease has been also reported in Australia, Haiti, India, and the USA. The organism is acquired through traumatic implantation and remains localized or spreads to infect other tissues, especially arteries. The diagnosis of the disease in humans is based in culture, serology, and histopathology. In all cases, hyphae of this oomycete are present in the infected tissues. Serological test such as ID and ELISA have proved to be of value for its early diagnosis.

Treatment of human subcutaneous pythiosis insidiosi on limbs, in which the arteries have been involved, consists of the amputation in the affected extremity. Iodides and other drugs have been used with questionable results. More recently the vaccine used to treat equine pythiosis, was successfully used in at least two cases of human pythiosis. The vaccine is being investigated for its possible use in new cases of human and animal pythiosis insidiosi.

Infections caused by this microorganism should no longer be considered rare in equines and companion animals. Dog and cat owners inhabiting endemic areas should consult their DVM practitioners when their pets present ulcerative cutaneous lesions or severe weight loss, vomiting, and diarrhea, for possible pythiosis insidiosi infection. I call this organism "the silent killer of mammals" because its true etiology was only recently being considered as a differential diagnosis with other similar clinical entities. The more we know about *P. insidiosum* infections and treatment the better prepared we are in preventing the disease and saving lives.

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***Clavibacter michiganense* subsp. *insidiosum* (McCulloch 1925)  
Davis et al. 1984<sup>VP</sup>**

**Basonym:** *Corynebacterium insidiosum* (Bacteria)

**DSM No.20157**

= ATCC 10253, NCPPB 1109

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<- ATCC <- W.H. Burkholder <- E.D. Hansing. **Type strain.** Taxonomy/description (1300, 3828, 4641). Murein: B7 (393). (Medium 53, 30°C).

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**Medium:** 53 . Reference(s): 393 , 419 , 1300 , 3828 , 4641

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**Normal price.**

